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10/613,390	07/03/2003	Zhifang Zhu	13552US	3338

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,390	ZHU ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Upon further consideration the species election requirement between the is withdraw, since no search burden was imposed on the Examiner to search allof them together.

Claims 1-21 are pending.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the instant application is not identified by the application number and by its filing date.

Claim Rejections - 35 USC § 112 – written description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3 and 5-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

When the claim is analyzed in light of the specification, the single-stranded oligonucleotide can be any randomly generated oligonucleotide (p. 11, lines 15-21). The specification discloses that the oligonucleotide is not particularly limited by its structure or function, needs not be designed to hybridize with any specific cellular sequences and if a sufficiently large number of such randomly generated oligonucleotides are administered at once it is likely that they will bind to a sufficient number of DNA-binding proteins to inhibit DNA replication (p. 11, lines 23-30). The genus, i.e., the single-stranded oligonucleotide, is described by its function to affect DNA replication, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally, the specification does not describe what would have been the identifying

characteristics, such as specific features and functional attributes, of the different oligonucleotides. In conclusion, this limited information is not sufficient to reasonably convey to one of ordinary skills in the art that the Applicants invented what was claimed. Consequently, the Applicants were not in possession of the instant claimed invention, at the time the application was filed.

Claims 12-14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

When the claim is analyzed in light of the specification, the oligonucleotide is not particularly limited by its structure, i.e., it can be any oligonucleotide, as long as it contains one or more regulatory elements capable of binding DNA-binding proteins, wherein the elements could be selected from a broad group consisting of various RNA polymerase-binding elements, various transcription factor-binding elements, various activator-binding elements, various repressor-binding elements, various GC-rich regions, and various nucleotide-binding protein-binding elements (p. 13, lines 20-32, p. 14, lines 1-4). Therefore, any oligonucleotide comprising one or more regulatory elements that interact with DNA-binding proteins could be claimed as an agent for the modulation of transcription in a cell. The genus, i.e., the oligonucleotide, is described by its function to modulate transcription, but the specification does not provide any

disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally, the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different oligonucleotides. It is acknowledged that the specification provides one example of using such an oligonucleotide to inhibit transcription, however providing one example is not sufficient to demonstrate that the Applicants were in possession of the whole genus. In conclusion, this limited information is not sufficient to reasonably convey to one of ordinary skills in the art that the Applicants invented what was claimed. Consequently, the Applicants were not in possession of the instant claimed invention, at the time the application was filed.

Claim Rejections - 35 USC § 112 - enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The Breadth of the Claims

The instant claims are drawn to (i) a method of treating a subject having a proliferative disorder by administering, in a subject, a single-stranded oligonucleotide capable to bind one or more DNA-binding proteins.

The aspects considered broad are: (i) the range of proliferative disorders to be treated, and (ii) the range of oligonucleotides (ODNs) used to treat the proliferative disorders.

When read in light of the specification, the breadth of the claimed ODNs clearly embraces any randomly generated ODN or any ODN comprising regulatory elements selected from a very wide variety of regulatory elements.

The broad term proliferative disorder is not limited in any way by the specification, and in fact encompasses distinct diseases that are caused by different genetic factors and result in different clinical manifestation. For example, the term embraces benign prostatic hyperplasia, disorders associated with an overgrowth of

connective tissue, such as abnormal scar formation and various fibrotic conditions, including arthritis, inflammatory bowel disease, psoriasis, and neoplastic disorders.

As such, the as-filed specification attempt to claim that the disclosed ODNs, as listed above, can be employed as a master drug to treat any cell proliferative disorder.

As will be shown below, these broad aspects are not enabled.

The Nature of the Invention

The nature of the invention is a method of treating proliferative disorders by using ODNs, wherein the ODNs are capable of inhibiting cell proliferation by binding one or more cellular DNA-binding proteins (i.e., decoy ODNs).

The nature of such invention is within the broad genera of gene therapy for proliferative disorders and gene therapy for proliferative disorders does not generally enable Applicants' invention due to problems with the complexity and unpredictability of such disorders and, also due to problems with using ODN-based therapies, such as specific delivery and intracellular stability (see Kalota et al., Cancer Biology & Therapy, 2004, 3: 4-12).

Applicants contemplate to use randomly generated single-stranded decoy ODNs to treat proliferative disorders. The specification discloses that these ODN need not be designed to bind to any specific nucleic acid sequence within the cell. Applicants envision that the administration, at once, of a large number of such oligonucleotides is enough to ensure that a sufficient number will bind to the cellular DNA-binding proteins with a resultant inhibition of cell proliferation. However, these approaches do not appear to be restricted to tumor cells. The specification discloses that the ODNs are

administered via direct injection into a region of cells afflicted with the proliferative disorder or systemically, without any reference of targeted delivery to the afflicted cells only or, once inside the cell, specific targeting to and retention into the nucleus. How will therapeutic apply in this case? Tumor-targeting agents are needed to differentiate between normal and malignant forms of the same tissue. While it is true that a growing number of transcription factors and activator of transcription have been identified to play a role in the pathogenesis of a wide variety of proliferative disorders, the same factors also play an important role in the normal cells; therefore, in the absence of specific targeting to the diseased cells, it is likely that the proliferation of the normal cells will also be inhibited. Mann et al. (J Clin Invest, 2000, 106: 1071-1075) teach:

> "Specificity becomes an even greater challenge when the target gene expression is to be inhibited in a single organ or tissue type, since systematic delivery of the DNA is likely to lead to widespread uptake and potential nonspecific side effects. In addition, as with other ODN strategies, the successful use of transcription factor decoys will almost always depend on an efficient means to deliver the synthetic DNA to target cell."

Redenti et al. (Advanced Drug Delivery Reviews, 2001, 53: 235-244) teach:

> "Following systemic administration, ODNs are distributed to all major peripheral organs, with the liver and kidneys accumulating the most. Several approaches have been proposed to increase the cellular uptake and biological activity of ODNs. However, their effective in vivo will require a more specific method to deliver them to the target cell population."

Additionally, without the ability to target the decoy oligonucleotide to the nucleus, it is likely that they are no going to be efficient. Along these lines, Gewirtz et al. (Proc Natl Acad Sci USA, 1996, 93: 3161-3163) teach:

> " After internalization, confocal and electron microscopy studies have indicated that the bulk of the ODNs enter the endosome/lysosome compartment. These vesicular structures may become acidified and acquire other enzymes that degrade the ODNs.

> Biologic inactivity is the predictable result of this process.
>
> Regardless, some of the ODNs clearly escape from the vesicles intact, enter the nucleus where presumably acquire their mRNA, or gene target. The processes that control release from the vesicles and regulate trafficking between the nucleus and the cytoplasm are not well understood.
>
> It is clear however that in addition to nuclear uptake, which is likely by passive diffusion through the nuclear pores, efflux from the nucleus also takes place. Therefore, sequestration of the ODNs in the endosome-lysosome compartment and efflux from the nucleus are significant problems that must be overcome in order for the technique to work reproducibly from cell type to cell type."

Therefore, the successful use of decoy oligonucleotides depends on an efficient means to deliver them to the target tissues or cells and of course, once inside the cell, to the nucleus, since they require nuclear localization to exert their function, i.e., binding to the transcription factors and activators. However, the specification does not provide any guidance on how these essential aspects are achieved.

In view of the reasons set forth above and of numerous issues, as indicated above, which need to be overcome in order to achieve the broadly claimed objective of the claimed subject matter, a skilled artisan would reasonably conclude that the state of the art of therapy of proliferative disorders by employing decoy ODNs to treat any cell proliferative disorder, remains reasonably unpredictable at the time of filing. Opalinska et al. (Nature Reviews Drug Discovery, 2002, 1: 504-514) teach:

> "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets.
>
> Short, double-stranded (ds) DNA decoy molecules have also been used to disrupt gene expression at the level of transcription. These oligodeoxynucleotides are designed to compete for transcription factor complexes, with the ultimate goal of attracting them away from the promoter that they ordinarily activate. For many technical reasons, including gene accessibility in the nucleosome structure, the clinical application of these

methods has not progressed at a rapid rate."

The Amount of Direction or Guidance/The Existence of Working Examples

Given the breadth of the claimed invention, and the complexities associated with the nature of the claimed invention, one skilled in the art would have to turn to the specification for guidance. However, as indicated above, and even assuming that the level of one skilled in the art is relatively high in the prior art, the guidance provided by the specification is not sufficient to overcome the doubts and obstacles expressed in the art of record. As such, the only issue left is the working examples provided by the specification.

Example 1 provides in vitro results showing inhibition of cell proliferation when the decoy ODNs are present.

Example 2 provides a protocol wherein a mixture of randomly generated ODNs and one decoy ODN consisting of regulatory elements is subcutaneously administered to melanoma mice models, however, it is clear from the Fig. 2 that the treated mice are dying short time after the control mice.

Example 3 provides a protocol wherein a randomly generated ODN and a one decoy ODN consisting of regulatory elements are intravenously administered to leukemia ascites mice models; in this protocol treated mice survived 35 days after the onset of the treatment; however, no data is provided with regard to the survival rate after day 35.

Therefore, these examples support the general concept that the art of using decoy ODNs is unpredictable because of the randomness with which these ODNs

modulate the expression of their intended targets (see Opalinska above).

The specification does not provide examples of testing the chimeric polypeptide for its ability to treat cancer in animal models or humans.

The examples provided by the specification do not appear to reasonably render the claimed invention as a whole patentable under 35 USC, 112, first paragraph, particularly given the doubts expressed by numerous cited art, as indicated above. Although the prior art teach that decoy ODNs targeted to specific factors can inhibit cell proliferation in cell cultures and in animal models, it is not apparent how this reasonably correlates with a successful targeted cancer therapy wherein unspecific decoy ODNs consisting of regulatory elements and randomly generated ODNs are delivered in sufficient amount and in such a way as to produce only targeted killing effects in the cancer cells. Gura (Science, 1997, 278: 1041-1042) teaches:

> "Screening potential anticancer drugs sounds easy. Just take a candidate drug, add it to a tumor type of choice, and then monitor whether the agent kills the cells or inhibits cancer growing. Too bad it hasn't been so simple.
>
> The fundamental problem in drug discovery for cancer is that the model systems are not predictive.
>
> The animals apparently do not handle the drugs exactly the way the human body does. And attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor site."

Along the same lines, Van Dyke et al. (Cell, 2002, 108: 135-144) teach:

> "However, a common feature of many mouse tumor models is that they represent mainly the early stages of disease development and relatively few recapitulate the features of advanced human cancer, including high frequency metastasis."

Therefore, the specification does not does not provide the guidance or the working examples required to overcome the art-recognized unpredictability of using ODNs to treat proliferative disorders in general. The field of using these ODNs as potential therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Given the diverse and unpredictable outcome of using the disclosed therapy method, the specification does not appear to provide sufficient guidance and/or working examples that specifically address the use of this method as being effective in treating proliferative disorders in patients to enable one of ordinary skill in the art to use such identification method without undue experimentation.

Conclusion

In conclusion, the specification is not enabling for the broad claims of a method of treating a subject having a proliferative disorder by administering, in a subject, a single-stranded oligonucleotide capable to bind one or more DNA-binding proteins.

While the intent is not to say that such decoy ODNs can never be used to treat proliferative disorders, the intent is to provide art taught reasoning as to why the instant claims are not enable to their full scope. In order to practice the claimed invention *in vivo* in a patient a number of variables would have to be optimized, including: (i) the delivery mode of the decoy ODNs to an organism that would allow it to specifically reach the targeted cell, (ii) the amount of decoy ODN that would need to be delivered in sufficient amount for the treatment, once it reached the proper cell, (iii) ensuring that the decoy ODNs are stable for a period of time that allows for a measurable and significant

therapeutic effect, and (iv) targeting and retention of the decoy ODN in the cell nucleus. Each one of these variables would have to be empirically determined. Optimization of any single one of these steps is not routine, and, when taken together, the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-3 and 5-14 are not enabled.

7. Claims 12-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulating transcription in a cell *in vitro* by administering to a cell an oligonucleotide consisting of one or more regulatory elements, wherein the regulatory elements are capable to bind a DNA-binding protein, does not reasonably provide enablement for modulating transcription in a cell by administering the above-mentioned oligonucleotide to cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants contemplate using decoy ODNs consisting of one or more regulatory elements capable of interacting with DNA-binding proteins to modulate transcription in any subject that has the ability to transcribe RNA from DNA, wherein the subject can be an organism or a cell. The nature of the invention is a method of inhibiting cell proliferation by using decoy ODN that reads on a method of treating proliferative cell disorders in a subject by administering the decoy ODN and treating proliferative cell disorders does not generally enable Applicants' invention due to problems with the

complexity and unpredictability of such disorders and also due to problems with using ODN-based therapies, such as specific delivery and intracellular stability. Therefore the rejection of claims 10-11 as indicated above is also applied to claims 12-21.

In conclusion, the presently claimed invention only provides enough of a disclosure to allow for an artisan to modulate transcription in a cell *in vitro* by contacting the cells with a decoy ODN comprising one or more regulatory elements capable of binding a DNA-binding protein.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 12-16, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Cho-Chung et al. (Current Opinion in Molecular Therapeutics, 1999, 1: 386-392).

Cho-Chung et al. teach modulating transcription in a cell by using decoy ODNs capable of inhibiting cell proliferation, wherein the decoy ODNs comprise one or more regulatory elements capable to bind transcription factors, i.e., DNA-binding proteins (see entire paper). With respect to the different ODNs lengths, this is not innovative over the prior art, the ordinary skilled artisan would have known to vary the lengths in a given method with the purpose of optimizing the results. Again, absent evidence to the

contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. Since Cho-Chung et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER

Ileana Popa